Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-006625-14	
Name of active ingredient: Olodaterol (BI 1744 CL)		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 04 APR 2012	**Trial No. / U No.:** 1222.29 / U12-1132-01	**Dates of trial:** 07 MAR 2011 – 19 DEC 2011	**Date of revision:** Not applicable

Title of trial:	Phase II, Randomised, Double-Blind, Cross-over Study to Compare the 24-hour FEV_1-time Profile of Orally Inhaled Olodaterol, delivered with the Respimat® Inhaler, after 3 Weeks of Olodaterol Once Daily 5 µg [2 actuations of 2.5 µg], Twice Daily 2.5 µg [2 actuations of 1.25 µg] and Placebo or after 3 Weeks of Once Daily 10 µg [2 actuations of 5 µg], Twice Daily 5 µg [2 actuations of 2.5 µg] and Placebo Administration in Patients with Moderate to Severe Persistent Asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multinational trial at 36 sites in Europe and North America
Publication (reference):	Data from this trial have not been published
Clinical phase:	II
Objectives:	The primary objective of the trial was to compare the 24-h FEV_1-time profile of olodaterol versus placebo after 3 weeks of once daily (5 µg, 10 µg) or twice daily (2.5 µg and 5 µg) olodaterol inhalation solution administration with the Respimat® inhaler. The secondary objective was to conduct an exploratory comparison between the different active treatments.
Methodology:	Randomised, placebo-controlled, double-blind, 3-period complete block crossover study with 5 possible treatments with patients assigned randomly to one of 12 treatment sequences with either 5 µg olodaterol once daily and 2.5 µg olodaterol twice daily and placebo (6 sequences) or 10 µg olodaterol once daily and 5 µg olodaterol twice daily and placebo (6 sequences).

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No. of patients:	
planned:	entered: 180
actual:	enrolled: 279 entered: 206 Placebo: treated: 201, analysed (for primary endpoint): 200 Olodaterol 2.5 µg b.i.d.: treated: 101, analysed (for primary endpoint): 99 Olodaterol 5 µg q.d.: treated: 101, analysed (for primary endpoint): 99 Olodaterol 5 µg b.i.d.: treated: 101, analysed (for primary endpoint): 100 Olodaterol 10 µg q.d.: treated: 102, analysed (for primary endpoint): 101 Since this was a crossover trial and every patient was supposed to receive 3 treatments, the total number of patients is not the sum of the number of patients on each treatment.
Diagnosis and main criteria for inclusion:	Moderate to severe persistent asthma; outpatients of either sex, aged ≥18 to ≤70 years with a current diagnosis and a documented history of asthma of at least 3 months (Global Initiative for Asthma [GINA] steps 3 and 4); pre-bronchodilator FEV_1 ≥60% and <90% of the predicted FEV_1 (calculated according to ECSC) and an increase in FEV_1 of at least 12% and at least 200 ml 15 min after administration of 400 µg salbutamol (albuterol) at the Screening Visit.

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Test product:	Olodaterol (BI 1744 CL) inhalation solution delivered by the Respimat® inhaler
dose:	2.5 µg (ex mouthpiece [2 actuations of 1.25 µg]) twice daily 5 µg (ex mouthpiece [2 actuations of 2.5 µg]) once daily in the morning 5 µg (ex mouthpiece [2 actuations of 2.5 µg]) twice daily 10 µg (ex mouthpiece [2 actuations of 5.0 µg]) once daily in the morning (calculated as free base)
mode of admin.:	Oral inhalation
batch no.:	Inhalation solution - Respimat® inhalers: B092000022 / 902873 - B092000043 / 9L0007 (1.25 µg/actuation) B072000346 / 710442 - B082000007 / 7L0058 (2.5 µg/actuation) B102000090 / 004332 - B082000022 / 7L0056 (2.5 µg/actuation) B072000356 / 710575 - B072000354 / 7L0057 (5 µg/actuation) B102000094 / 004372 - B082000022 / 7L0056 (5 µg/actuation)
Reference therapy:	Placebo inhalation solution delivered by the Respimat® inhaler
dose:	Not applicable
mode of admin.:	Oral inhalation
batch no.:	Inhalation solution - Respimat® inhalers: B082000136 / 806379 - B072000350 / 7L0056 B082000136 / 806379 - B082000022 / 7L0056
Duration of treatment:	A 2-week baseline period, 3 x 3-week treatment periods (total treatment duration of 9 weeks) separated by 2-week washout periods, and a 2-week follow-up period after study drug termination. Patients had to take ICS throughout the trial as background medication.

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Criteria for evaluation:

Efficacy:

Primary endpoint
FEV_1 area under the curve from 0-24 h (AUC_{0-24}) after 3 weeks of treatment, divided by 24 h to report in litres; study baseline FEV_1.(assessed before administration of any trial treatment) was subtracted from the FEV_1 AUC_{0-24} at the end of each 3-week treatment period. This quantity is subsequently referred to as FEV_1 AUC_{0-24} response at the end of each 3-week treatment period.

Key secondary endpoints
FEV_1 AUC_{0-12} response and FEV_1 AUC_{12-24} response at the end of each 3-week treatment period

Further secondary endpoints
Clinic spirometry at the end of each 3-week treatment period: Forced vital capacity (FVC) AUC_{0-24} response, FVC AUC_{0-12} response, FVC AUC_{12-24} response, peak expiratory flow (PEF) AUC_{0-24} response, PEF AUC_{0-12} response, PEF AUC_{12-24} response, peak FEV_1 response within 24 h post-dose, peak FVC response within 24 h post-dose, peak PEF response within 24 h post-dose, trough FEV_1 response, trough FVC response, trough PEF response; individual FEV_1, FVC, and PEF values at the following time points relative to a m. trial drug administration: -1:00, -0:10, 0:30, 1:00, 2:00, 3:00, 4:00, 6:00, 8:00, 10:00, 11:50, 12:30, 13:00, 14:00, 22:00, 23:00, 23:50

Clinic spirometry at the beginning of the treatment periods: FEV_1 AUC_{0-3} response, FVC AUC_{0-3} response, PEF AUC_{0-3} response, peak FEV_1 response within 3 h post-dose, peak FVC response within 3 h post-dose, peak PEF response within 3 h post-dose

Patient diaries: For each treatment period, weekly and overall means of the following parameters: morning PEF, evening PEF, PEF daily variability, morning FEV_1, evening FEV_1, use of rescue medication over 24 h, nighttime use of rescue medication, daytime use of rescue medication; weekly and overall worst category of number of nighttime awakenings and daytime and nighttime asthma symptoms; percentage of asthma symptom-free days

Questionnaires: Total Asthma Control Questionnaire (ACQ) score at the end of each 3-week treatment period

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Safety:	Adverse events (AEs), vital signs (pulse rate and blood pressure), routine blood chemistry, haematology and urinalysis, 12-lead electrocardiogram (ECG)
Statistical methods:	The primary endpoint was analysed using a mixed model with treatment, period, and study baseline FEV_1 as fixed effects, and patient as a random effect. Continuous secondary endpoints were analysed similarly to the primary endpoint. Other secondary endpoints and safety endpoints were summarised descriptively only.

SUMMARY – CONCLUSIONS:

Efficacy results:

Out of the 206 treated patients, 199 patients (96.6%) completed the planned treatment time in all 3 treatment periods, i.e. 7 patients (3.4%) discontinued study treatment prematurely. The number of patients who stopped study treatment was 1 or 2 for each treatment (0.5% to 2.0%). The most frequent reason for premature discontinuation was non-compliance with the trial protocol (1 patient on each of 3 treatments). The treated population consisted mainly of White patients (92.7%); the overall proportion of female patients was 52.9%. The mean age in the treated set was 43.7 years and the mean duration of asthma was 24.7 years. More than half of the patients had had asthma for at least 20 years (60.2%).

For the primary endpoint FEV_1 AUC_{0-24} response after 3 weeks of treatment, the adjusted mean treatment difference vs. placebo was 0.191 L for treatment with 2.5 µg olodaterol b.i.d. (95% CI 0.152, 0.229), 0.150 L for 5 µg olodaterol q.d. (95% CI 0.111, 0.189), 0.228 L for 5 µg olodaterol b.i.d. (95% CI 0.190, 0.266), and 0.209 L for 10 µg olodaterol q.d. (95% CI 0.170, 0.247). The mean differences between each olodaterol treatment and placebo were highly statistically significant ($p<0.0001$). Thus, for the primary endpoint mean FEV_1 AUC_{0-24} response, olodaterol treatment was superior to placebo for all doses and dose regimens administered. These results were supported by several sensitivity analyses. Analyses of the key secondary endpoints FEV_1 AUC_{0-12} response and FEV_1 AUC_{12-24} response showed consistent results with those for the primary endpoint. With regard to the primary endpoint as well as the key secondary endpoints, the treatment effect of olodaterol increased with the daily olodaterol dose at both dosing frequencies. With regard to the primary endpoint, the adjusted mean differences (q.d. - b.i.d.) were -0.040 L (95% CI -0.080, 0.001;

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Efficacy results: (continued)

p=0.0465) for the daily dose of 5 µg olodaterol and -0.019 L (95% CI -0.059, 0.020; p=0.3388) for the daily dose of 10 µg olodaterol. Both mean FEV_1 peak and trough responses were highly statistically significantly different from placebo ($p<0.0001$) for all doses of olodaterol and increased with the daily olodaterol dose at both dosing frequencies. Adjusted mean FEV_1 values at individual time points pre- and post-dose showed efficacy of all olodaterol doses and frequencies at each point over the 24-h interval with results which were consistent with those from the summary measures defined over the 24-h FEV_1 curve. Secondary endpoints derived from FVC and PEF measurements at clinic visits after 3 weeks of treatment were broadly consistent with the results of FEV_1 endpoints.

Weekly and overall mean morning and evening PEF and FEV_1 measurements at home using the AM3® device showed improvements in mean compared with placebo for all olodaterol treatments. Therefore, results were consistent with the results of endpoints derived from FEV_1 and PEF measured at the clinic visits after 3 weeks of treatment.

AUC_{0-3} responses and peak responses derived from FEV_1, FVC, and PEF measurements at clinic visits at the start of treatment showed evidence of superiority ($p<0.0001$ for FEV_1 endpoints) of all olodaterol doses over placebo after single administration (2.5 µg, 5 µg, and 10 µg).

Safety results:

The mean exposure to study treatment was comparable for all treatments, ranging from 22.8 days both 2.5 µg olodaterol b.i.d. and 5 µg olodaterol b.i.d. to 23.4 days for treatment with placebo. The mean total exposure to study medication (excluding washout periods between treatments) was 67.9 days.

The overall frequency of patients who reported at least 1 AE whilst on treatment was 35.4% (placebo: 16.4%, 2.5 µg b.i.d.: 14.9%, 5 µg q.d.: 14.9%, 5 µg b.i.d.: 18.8% and 10 µg q.d. olodaterol: 12.7%). The most common treatment-emergent AEs by SOC were infections and infestations with sinusitis as the most frequently reported AE within this SOC and respiratory, thoracic, and mediastinal disorders with asthma as the most frequently reported AE within this SOC. The most frequent AEs on the preferred term level were headache and asthma; the incidence of both was low for all treatments. By-gender analysis revealed no relevant difference in the frequency of male and female patients with any AE (34.0% and 36.7%, respectively). Adverse events in 7 patients (3.4%)

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Safety results: (continued)	were considered treatment-related by the investigators; 5 of these patients were receiving olodaterol at the onset of the AE, 4 of them a daily dose of 10 µg olodaterol (5 µg b.i.d. or 10 µg q.d.). The most frequent AE considered drug-related was cough (3 patients). Four patients (1.9%) experienced SAEs during the study; fall, laceration, and concussion (all on the same patient) on treatment with 2.5 µg olodaterol b.i.d., gastroenteritis on treatment with 5 µg olodaterol b.i.d., and diverticulitis in 1 patient and meniscus lesion in another patient on treatment with placebo. All patients recovered from the SAEs and no SAE was considered study drug-related. Other significant AEs were reported for 2 patients, in both cases non-serious AEs that led to discontinuation of trial treatment, one of them (exacerbation of asthma) was considered to be related to study treatment. No notable findings with regard to assessment of laboratory parameters, vital signs, and ECG recordings were observed.
Conclusions:	All doses and dose regimens of olodaterol (2.5 µg b.i.d., 5 µg q.d., 5 µg b.i.d., 10 µg q.d.) showed superiority over placebo with regard to the mean FEV_1 AUC_{0-24} response after 3 weeks of treatment in this crossover trial in patients with asthma. Furthermore, dose-ordering for the mean FEV_1 AUC_{0-24} response was observed with increasing daily dose at both dosing frequencies. For the same daily dose, twice daily administration resulted in a numerically higher response than once daily dosing, with only a minimal difference at the 10 µg daily dose. The results of this study support the 24-h duration of bronchodilation induced by olodaterol as FEV_1 was highly statistically significantly different from placebo at every single time point for 24 h after once daily administration of olodaterol in the morning for both daily doses investigated, with mean differences which were clinically relevant. These results were broadly supported by the results of the secondary endpoints derived from clinic visits and home-based spirometry measurements. The results of this study showed that olodaterol was generally safe and well tolerated. The overall frequency of patients with AEs for all olodaterol treatments was comparable to that for placebo treatment. Furthermore, assessment of laboratory parameters and vital signs did not reveal any clinically significant differences from placebo treatment.

Trial Synopsis – Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The number of secondary endpoints defined for this trial was too large to allow meaningful presentation in this format. The appended tables provide complete disposition results and results of additional secondary endpoints, as summarized below.

Results for	**presented in**
Disposition of patients	Table 15.1.1: 1
FEV_1 $AUC_{0\text{-}24h}$ response after 4 weeks FEV_1 $AUC_{0\text{-}12h}$ response after 4 weeks FEV_1 $AUC_{12\text{-}24h}$ response after 4 weeks	Table 15.2.1.1: 1
Peak FEV_1 response (within 24 hours after dosing) after 4 weeks	Table 15.2.1.3: 1
Trough FEV_1 response (within 24 hours after dosing) after 4 weeks	Table 15.2.1.4: 1
FVC $AUC_{0\text{-}24h}$ response after 4 weeks FVC $AUC_{0\text{-}12h}$ response after 4 weeks FVC $AUC_{12\text{-}24h}$ response after 4 weeks	Table 15.2.2.1: 1
PEF $AUC_{0\text{-}24h}$ response after 4 weeks PEF $AUC_{0\text{-}12h}$ response after 4 weeks PEF $AUC_{12\text{-}24h}$ response after 4 weeks	Table 15.2.3.1: 1

Table 15.1.1: 1 Disposition of patients

	Placebo	Olo 2.5ug bd	Olo 5ug qd	Olo 5ug bd	Olo 10ug qd	Total
Enrolled						279
Not entered/randomised						73
Entered/randomised						206
Treated	201(100.00)	101(100.00)	101(100.00)	101(100.00)	102(100.00)	206(100.00)
Not prematurely discontinued from trial medication	200(99.50)	99(98.02)	99(98.02)	100(99.01)	101(99.02)	199(96.60)
Prematurely discontinued from trial medication	1(0.50)	2(1.98)	2(1.98)	1(0.99)	1(0.98)	
Adverse event	0(0.00)	1(0.99)	0(0.00)	1(0.99)	0(0.00)	
AE study dis. worse	0(0.00)	0(0.00)	0(0.00)	1(0.99)	0(0.00)	
AE-other	0(0.00)	1(0.99)	0(0.00)	0(0.00)	0(0.00)	
Non compl prot.	1(0.50)	1(0.99)	0(0.00)	0(0.00)	1(0.98)	
Consent withdrawn	0(0.00)	0(0.00)	2(1.98)	0(0.00)	0(0.00)	

Table 15.2.1.1: 1 Adjusted mean* (SE) FEV1 AUC(0-12), AUC(12-24) and AUC(0-24) response [L] and comparisons to placebo after 3 weeks - analysis with imputation (FAS)

Time interval	Treatment	N	Treatment mean (SE)	Difference to Placebo		
				Mean (SE)	P-value	95% CI
0-12 hr	Placebo	200	0.052 (0.020)			
	Olo 2.5ug bd	99	0.242 (0.024)	0.190 (0.020)	<.0001	(0.150, 0.229)
	Olo 5ug qd	99	0.212 (0.024)	0.160 (0.020)	<.0001	(0.121, 0.199)
	Olo 5ug bd	100	0.266 (0.024)	0.214 (0.020)	<.0001	(0.175, 0.253)
	Olo 10ug qd	101	0.272 (0.024)	0.219 (0.020)	<.0001	(0.181, 0.258)
12-24 hr	Placebo	201	-0.010 (0.020)			
	Olo 2.5ug bd	99	0.186 (0.025)	0.196 (0.022)	<.0001	(0.153, 0.238)
	Olo 5ug qd	99	0.135 (0.025)	0.144 (0.022)	<.0001	(0.102, 0.187)
	Olo 5ug bd	100	0.233 (0.025)	0.242 (0.022)	<.0001	(0.200, 0.285)
	Olo 10ug qd	101	0.189 (0.025)	0.198 (0.022)	<.0001	(0.156, 0.241)
0-24 hr	Placebo	200	0.022 (0.020)			
	Olo 2.5ug bd	99	0.213 (0.024)	0.191 (0.020)	<.0001	(0.152, 0.229)
	Olo 5ug qd	99	0.173 (0.024)	0.150 (0.020)	<.0001	(0.111, 0.189)
	Olo 5ug bd	100	0.250 (0.024)	0.228 (0.020)	<.0001	(0.190, 0.266)
	Olo 10ug qd	101	0.231 (0.024)	0.209 (0.020)	<.0001	(0.170, 0.247)

*adjusted using a mixed model with treatment, period and study baseline value as fixed effects; and patient as a random effect.
Common study baseline mean (se): 0-12 hr = 2.571 (0.054), 12-24 hr = 2.571 (0.054), 0-24 hr = 2.571 (0.054)

Source data: Appendix 16.1.9.2, Statdoc 6.1.1 ctr\eot-t4-pft-adjmean-refcomp.sas 26JAN2012

Table 15.2.1.3: 1 Adjusted mean* (SE) FEV1 peak response [L] and comparisons to placebo after 3 weeks - analysis with imputation (FAS)

			Difference to Placebo		
Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
Placebo	201	0.227 (0.021)			
Olo 2.5ug bd	99	0.410 (0.027)	0.183 (0.023)	<.0001	(0.138, 0.228)
Olo 5ug qd	99	0.380 (0.027)	0.153 (0.023)	<.0001	(0.108, 0.198)
Olo 5ug bd	100	0.449 (0.027)	0.222 (0.023)	<.0001	(0.177, 0.267)
Olo 10ug qd	101	0.437 (0.026)	0.210 (0.023)	<.0001	(0.165, 0.255)

*adjusted using a mixed model with treatment, period and study baseline value as fixed effects; and patient as a random effect.
Common study baseline mean (se): 2.571 (0.054)

Source data: Appendix 16.1.9.2, Statdoc 6.1.6 ctr\eot-t4-pft-adjmean-refcomp.sas 26JAN2012

Table 15.2.1.4: 1 Adjusted mean* (SE) FEV1 trough response [L] and comparisons to placebo after 3 weeks - analysis with imputation (FAS)

			Difference to Placebo		
Treatment	N	Treatment mean (SE)	Mean (SE)	P-value	95% CI
Placebo	201	0.033 (0.022)			
Olo 2.5ug bd	99	0.189 (0.027)	0.156 (0.024)	<.0001	(0.109, 0.203)
Olo 5ug qd	99	0.134 (0.027)	0.101 (0.024)	<.0001	(0.054, 0.148)
Olo 5ug bd	100	0.229 (0.027)	0.196 (0.024)	<.0001	(0.149, 0.243)
Olo 10ug qd	101	0.205 (0.027)	0.172 (0.024)	<.0001	(0.125, 0.219)

*adjusted using a mixed model with treatment, period and study baseline value as fixed effects; and patient as a random effect.
Common study baseline mean (se): 2.571 (0.054)

Source data: Appendix 16.1.9.2, Statdoc 6.1.7 ctr\eot-t4-pft-adjmean-refcomp.sas 26JAN2012

Table 15.2.2.1: 1 Adjusted mean* (SE) FVC AUC(0-12), AUC(12-24) and AUC(0-24) response [L] and comparisons to placebo after 3 weeks - analysis with imputation (FAS)

Time interval	Treatment	N	Treatment mean (SE)	Difference to Placebo		
				Mean (SE)	P-value	95% CI
0-12 hr	Placebo	200	-0.004 (0.022)			
	Olo 2.5ug bd	99	0.132 (0.027)	0.136 (0.023)	<.0001	(0.091, 0.180)
	Olo 5ug qd	99	0.119 (0.027)	0.122 (0.023)	<.0001	(0.078, 0.167)
	Olo 5ug bd	100	0.138 (0.026)	0.142 (0.022)	<.0001	(0.098, 0.186)
	Olo 10ug qd	101	0.143 (0.026)	0.147 (0.022)	<.0001	(0.103, 0.191)
12-24 hr	Placebo	201	-0.056 (0.023)			
	Olo 2.5ug bd	99	0.102 (0.028)	0.158 (0.024)	<.0001	(0.110, 0.206)
	Olo 5ug qd	99	0.081 (0.028)	0.137 (0.024)	<.0001	(0.090, 0.185)
	Olo 5ug bd	100	0.114 (0.028)	0.170 (0.024)	<.0001	(0.123, 0.218)
	Olo 10ug qd	101	0.079 (0.028)	0.135 (0.024)	<.0001	(0.087, 0.182)
0-24 hr	Placebo	200	-0.029 (0.021)			
	Olo 2.5ug bd	99	0.116 (0.026)	0.145 (0.022)	<.0001	(0.102, 0.188)
	Olo 5ug qd	99	0.099 (0.026)	0.128 (0.022)	<.0001	(0.085, 0.171)
	Olo 5ug bd	100	0.127 (0.026)	0.156 (0.022)	<.0001	(0.113, 0.198)
	Olo 10ug qd	101	0.111 (0.026)	0.140 (0.022)	<.0001	(0.098, 0.182)

*adjusted using a mixed model with treatment, period and study baseline value as fixed effects; and patient as a random effect.
Common study baseline mean (se): 0-12 hr = 3.849 (0.073), 12-24 hr = 3.849 (0.073), 0-24 hr = 3.849 (0.073)

Source data: Appendix 16.1.9.2, Statdoc 6.2.1 ctr\eot-t4-pft-adjmean-refcomp.sas 26JAN2012

Table 15.2.3.1: 1 Adjusted mean* (SE) PEF AUC(0-12), AUC(12-24) and AUC(0-24) response [L/sec] and comparisons to placebo after 3 weeks - analysis with imputation (FAS)

Time interval	Treatment	N	Treatment mean (SE)	Difference to Placebo		
				Mean (SE)	P-value	95% CI
0-12 hr	Placebo	200	0.101 (0.060)			
	Olo 2.5ug bd	99	0.730 (0.075)	0.629 (0.065)	<.0001	(0.500, 0.757)
	Olo 5ug qd	99	0.703 (0.075)	0.601 (0.065)	<.0001	(0.473, 0.730)
	Olo 5ug bd	100	0.732 (0.074)	0.631 (0.065)	<.0001	(0.503, 0.758)
	Olo 10ug qd	101	0.787 (0.074)	0.685 (0.065)	<.0001	(0.558, 0.813)
12-24 hr	Placebo	201	-0.135 (0.061)			
	Olo 2.5ug bd	99	0.530 (0.077)	0.665 (0.068)	<.0001	(0.532, 0.799)
	Olo 5ug qd	99	0.430 (0.076)	0.564 (0.068)	<.0001	(0.431, 0.698)
	Olo 5ug bd	100	0.567 (0.076)	0.702 (0.068)	<.0001	(0.569, 0.835)
	Olo 10ug qd	101	0.464 (0.076)	0.599 (0.067)	<.0001	(0.467, 0.732)
0-24 hr	Placebo	200	-0.014 (0.059)			
	Olo 2.5ug bd	99	0.627 (0.073)	0.641 (0.063)	<.0001	(0.516, 0.765)
	Olo 5ug qd	99	0.563 (0.073)	0.577 (0.063)	<.0001	(0.453, 0.701)
	Olo 5ug bd	100	0.653 (0.073)	0.667 (0.063)	<.0001	(0.544, 0.790)
	Olo 10ug qd	101	0.629 (0.073)	0.643 (0.063)	<.0001	(0.519, 0.766)

*adjusted using a mixed model with treatment, period and study baseline value as fixed effects; and patient as a random effect.
Common study baseline mean (se): 0-12 hr = 6.936 (0.146), 12-24 hr = 6.936 (0.146), 0-24 hr = 6.936 (0.146)